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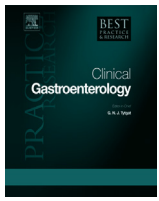

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Management of the patient with incomplete response to PPI therapy

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A B S T R A C T

Proton pump inhibitors (PPIs) remove most of the acid from the gastroesophageal refluxate. However, PPIs do not eliminate reflux and the response of specific GERD symptoms to PPI therapy depends on the degree to which acid drives those symptoms. PPIs are progressively less effective for heartburn, regurgitation, chest pain and extra-oesophageal symptoms. Hence, with an incomplete PPI response, obtaining an accurate history, detailing which symptoms are 'refractory' and exactly what evidence exists linking these symptoms to GERD is paramount. Reflux can continue to cause symptoms despite PPI therapy because of persistent acid reflux or weakly acidic reflux. Given these possibilities, diagnostic testing (pH or pH-impedance monitoring) becomes essential. Antireflux surgery is an alternative in patients if a clear relationship is established between persistent symptoms, particularly regurgitation, and reflux. Treating visceral hypersensitivity may also benefit the subset of GERD patients whose symptoms are driven by this mechanism.

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Introduction

Proton pump inhibitor (PPI) therapy has largely changed the clinical face of gastroesophageal reflux disease (GERD). Prior to the introduction of PPIs in 1989, clinicians struggled to manage reflux patients with the existing pharmacological therapies, dominated at the time by the histamine-2 receptor antagonists. Of course, the 'refractory patient' at that time was easily defined with an endoscope: persistent mucosal erosions, ulcers, and recurrent strictures. Almost miraculously, however, these problems succumbed to the potent acid suppression made possible with PPIs. It is now widely accepted that the mucosal manifestations of GERD (other than Barrett's metaplasia) can be controlled indefinitely with sustained PPI therapy [1]. Not surprisingly, PPI use has subsequently increased tremendously and a number of alternative molecules have been added to the therapeutic armamentarium.

The ensuing PPI euphoria broadened through the turn of the century leading many clinicians to conclude that, not only were these drugs tremendously effective in treating GERD, but that the therapeutic response to PPIs constituted a clinical definition of GERD [2]. If a patient's symptoms responded to PPIs, they had GERD and conversely, if they did not respond to PPIs, they did not have GERD. Or so the thinking went. This was, of course, flawed thinking, as it would equate to diagnosing rheumatoid arthritis based on improvement with aspirin therapy [3]. While it is true that many cases of rheumatoid arthritis do respond to aspirin, it is also true that many do not and, for that matter, that many other conditions may exhibit a therapeutic response to aspirin. And then there is the placebo response. The analogy with GERD is apparent.

The other evolution that has parallelled the introduction of PPIs, perhaps even made possible by the PPIs, was an improved understanding of the full spectrum of GERD. As the problem of refractory mucosal disease receded, the problem of refractory symptoms blossomed. And the list of symptoms and syndromes potentially attributable to GERD expanded. These developments led to the formation of an international consensus conference tasked with developing a modern definition of GERD. The resultant 'Montreal definition' proposed the overarching definition of GERD as 'a condition which develops when the reflux of stomach contents causes *troublesome* symptoms and/or complications' [4]. The consensus document went on to review health related quality of life data pertinent to the cardinal reflux symptoms, heartburn and regurgitation to define 'troublesome'. In the case of heartburn, the threshold at which the symptom becomes 'troublesome' as evident by a clinically relevant decrement in health related quality of life was $\geq$2 days/week of mild symptoms or $\geq$1 day/week of moderate symptoms. No thresholds were proposed for any other potential reflux symptoms because no relevant data could be found in the literature. Nonetheless, failure to satisfactorily resolve potential GERD symptoms has become one of the most common reasons for gastroenterological consultations in the US and Western Europe [5]. This treatise will explore the many facets of this clinical scenario and propose a systematic approach to management.

Phenotypes of incomplete PPI response

An estimated 10–40% of the patients with 'GERD' have either an incomplete or no response to a standard dose of PPI [6,7]. However, while that may be a unifying clinical diagnostic code, this is an extraordinarily heterogeneous group of patients. PPI therapy is, after all, directed at suppressing gastric acid secretion and acid secretion is usually normal in GERD patients. Rather, the primary pathophysiology of GERD usually resides in the domains of excessive or abnormal reflux events, prolonged acid clearance, or altered mucosal sensitivity as conceptualized in Fig. 1. Any of these may dominate the pathophysiology of a particular reflux syndrome. Indeed, even prior to treatment most patients with heartburn do not have reflux oesophagitis and this disconnect becomes more exaggerated in patients with atypical GERD symptoms. Furthermore, the dominant mechanism distinguishing oesophagitis from non-erosive reflux disease is not found in the number of reflux events but rather, in prolonged refluxate (acid) clearance mechanistically attributable to the effects of a hiatal hernia or weak peristalsis [9,10]. In fact, prolonged acid